

Amendments to the Specification:

Please replace the paragraph at page 5, lines 23-27 with the following amended paragraph:

The terms "plurality of cell lines" or "matrix of cell lines" refer to one or more sets of cell lines used, for example, in the preparation of a set of genetic response profiles. Exemplary pluralities of cell lines are described in, for example, PCT publication WO 01/71023 (application PCT/US01/08670, filed March 16, 2001), which is hereby incorporated by reference in its entirety.

Please replace the paragraph at page 7, line 21 through page 8, line 7 with the following amended paragraph:

Cell lines which can be used in the methods of the present invention include, but are not limited to, those available from cell repositories such as the American Type Culture Collection (~~www-~~on the World Wide Web at atcc.org), the World Data Center on Microorganisms (~~http://wdcm.nig.ac.jp~~), the European Collection of Animal Cell Culture (~~www-~~on the World Wide Web at ecacc.org) and the Japanese Cancer Research Resources Bank (~~http://cellbank.nihs.go.jp~~). These cell lines include, but are not limited to, HeLa cells, COS cells, lung carcinoma cell lines including squamous cell carcinoma cell lines (such as LK-2, LC-1, EBC-1, and NCI-H157), large cell carcinoma cell lines (such as H460 and H1299), small-cell carcinoma cell lines (such as H345, H82, H209, and N417); adenocarcinoma cell lines (such as A549, H322, H522, H358, H23 and RERF-LC-MS); fibrosarcoma cell lines (such as HT1080); prostrate cancer cell lines (e.g., PC3, DU145, LNCaP, MDA-PCa 2a, MDA-PCa 2b, ARCaP) and other cell lines commonly used by one of skill in the art (for example: 293, 293Tet-Off, CHO-AA8 Tet-Off, MCF7, MCF7 Tet-Off, LNCap, T-5, BSC-1, BHK-21, Phinx-A, 3T3, ZR 75-1, HS 578-T, DBT, Bos, CV1, L-2, RK13, HTTA, HepG2, BHK-Jurkat, Daudi, RAMOS, KG-1, K562, U937, HSB-2, HL-60, MDAH231, C2C12, HTB-26, HTB-129, HPIC5, A-431, CRL-1573, 3T3L1, Cama-1, J774A.1, HeLa 229, PT-67, Cos7, OST7, HeLa-S, THP-1, and NXA.) Additional cell lines for use in the methods and kits of the present invention can be obtained, for example, from cell line providers such as Clonetics Corporation (Walkersville, MD; ~~www-~~on the World Wide Web at clonetics.com).

Please replace the paragraph at page 11, line 26 through page 12, line 20 with the following amended paragraph:

A variety of mutagenesis protocols, such as viral-based mutational techniques, homologous recombination techniques, gene trap strategies, inaccurate replication strategies, and chemical mutagenesis, are available and described in the art. These procedures can be used

separately and/or in combination to produce modified cell lines for use in the methods of the present invention. See, for example, Amsterdam et al. "A large-scale insertional mutagenesis screen in zebrafish" *Genes Dev* 1999 Oct 13:2713-2724; Carter (1986) "Site-directed mutagenesis" *Biochem. J.* 237:1-7; Cramer and Stemmer (1995) "Combinatorial multiple cassette mutagenesis creates all the permutations of mutant and wildtype cassettes" *BioTechniques* 18:194-195; Inamdar "Functional genomics the old-fashioned way: chemical mutagenesis in mice" *Bioessays* 2001 Feb 23:116-120; Ling et al. (1997) "Approaches to DNA mutagenesis: an overview" *Anal Biochem.* 254(2): 157-178; Napolitano et al. "All three SOS-inducible DNA polymerases (Pol II, Pol IV and Pol V) are involved in induced mutagenesis" *EMBO J* 2000 Nov 19:6259-6265; and Rathkolb et al. "Large-scale N-ethyl-N-nitrosourea mutagenesis of mice--from phenotypes to genes" *Exp Physiol* 2000 Nov 85:635-44. Furthermore, kits for mutagenesis and related techniques are also available from a number of commercial sources (see, for example, Stratagene (~~http://www.~~on the World Wide Web at stratagene.com/vectors/index2.htm), Clontech (~~http://www.~~on the World Wide Web at clontech.com/retroviral/index.shtml), and the Gateway cloning system from Invitrogen (~~http://www.~~on the World Wide Web at invitrogen.com)). General texts which describe molecular biological techniques useful in the generation of modified cell lines, including mutagenesis, include Berger and Kimmel, *Guide to Molecular Cloning Techniques, Methods in Enzymology*, volume 152 Academic Press, Inc., San Diego, CA; Sambrook et al., *Molecular Cloning - A Laboratory Manual* (2nd Ed.), volumes 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1989; and *Current Protocols in Molecular Biology*, F.M. Ausubel et al., eds., Current Protocols, a joint venture between Greene Publishing Associates, Inc. and John Wiley & Sons, Inc., (supplemented through 2000)).

Please replace the paragraph at page 15, with the following amended paragraph:

Thus, the plurality of cell lines employed in the present invention can include a combination of parental or wildtype cells, singular-modification cells, multiply-modified cells, resistant cells, cells optimized for a particular disease state, and the like. Further details regarding the generation and use of pluralities of cell lines can be found in PCT publication WO 01/71023 (application PCT/US01/08670 ~~to~~ Monforte et al.), filed March 16, 2001.

Please replace the paragraph at page 18, lines 3-19 with the following amended paragraph:

RNA and proteins isolated from this small set of samples is analyzed using a number of broad scanning techniques as described below. From this analysis, as well as optional literature data, sets of genes/gene products (e.g. between about 10 and about 20, about 50, about 100 or about

1000) are selected for response profiling. Protein and nucleic acid sequences that can be monitored in the methods of the present invention include, but are not limited to, those listed with the National Center for Biotechnology Information (~~www-~~on the World Wide Web at ncbi.nlm.nih.gov) in the GenBank® databases, and sequences provided by other public or commercially-available databases (for example, the NCBI EST sequence database, the EMBL Nucleotide Sequence Database; Incyte's (Palo Alto, CA) LifeSeq™ database, and Celera's (Rockville, MD) "Discovery System"™ database). For example, proteins that can be monitored (e.g., as part of the genetic response profile) in the plurality of cell lines used in the present invention include, but are not limited to, signaling proteins, regulatory proteins, pathway specific proteins, receptor proteins, and other proteins involved in one or more biochemical pathways. Nucleic acids that can be monitored include, but are not limited to, DNA, genomic DNA, BAC or YAC constructs, viral DNA, plasmid DNA or other vectors, tRNA, rRNA, mRNA, guide RNA, snRNA molecules, snoRNA molecules, and hnRNA molecules.

Please replace the paragraph at page 20, lines 13-19 with the following amended paragraph:

Alternatively, high throughput screening systems utilizing microfluidic technologies, available, for example, from Agilent/Hewlett Packard (Palo Alto, CA) and Caliper Technologies Corp. (Mountain View, CA) could be employed for detecting the response(s) generated in the plurality of cell lines. The Caliper Lab Chip™ technology uses microscale microfluidic techniques for performing analytical operations such as the separation, sizing, quantification and identification of nucleic acids (for further information, see ~~www-~~on the World Wide Web at calipertech.com).

Please replace the paragraph at page 23, lines 12-25 with the following amended paragraph:

Multivariate statistics, such as principal components analysis (PCA), factor analysis, cluster analysis, n-dimensional analysis, difference analysis, multidimensional scaling, discriminant analysis, and correspondence analysis, can be employed to simultaneously examine multiple variables for one or more patterns of relationships (for a general review, see Chatfield and Collins, "Introduction to Multivariate Analysis," published 1980 by Chapman and Hall, New York; and Höskuldsson Agnar, "Predictions Methods in Science and Technology," published 1996 by John Wiley and Sons, New York). Multivariate data analyses are used for a variety of applications involving these multiple factors, including quality control, process optimization, and formulation determinations. The analyses can be used to determine whether there are any trends in the data collected, whether the properties or responses measured are related to one another, and which properties are most relevant in a given context (for example, a disease state). Software for statistical

analysis is commonly available, e.g., from Partek Inc. (St. Peters, MO; see ~~www.~~on the World Wide Web at partek.com).

Please replace the paragraph at page 25, lines 8-20 with the following amended paragraph:

The methods of the present invention can be used in the development of novel chemotherapeutics for cancer treatment. The methods employ one or more modified cancer cell lines prepared as follows. One or more cancer cell lines are selected, ~~and~~ challenged with a chemotherapeutic agent (e.g. methotrexate or cisplatin), and ~~allowing the cells~~ the cells are allowed to grow. Different dosing techniques may be used, for example, increasing the dosage of the agent over multiple cell cycles, using multiple doses of the same concentration over multiple cycles, or just using a single dose of the agent. Modified cells that are capable of growth in the dosed environment are selected. These modified cells have developed a resistance to the particular compound, i.e. they have a different response to the primary activity of the compound versus the parent cell line. Cells that survive the challenge with the chemotherapeutic agent can be individually selected and grown clonally for inclusion in the plurality of cell lines. Optionally, the new cell line is treated with the chemotherapeutic agent to confirm its resistance.